Bristol-Myers Squibb
Pharmaceutical Research Institute

P.O. Box 4000, Princeton, NJ 08543-4000
609-252-5638 Fax: 609 252-6425
laurie.smaldone@bms.com

Laurie Smaldone, M.D.
Regulatory Science and Outcomes Research

November 1, 2000

Dockets Management Branch
Food and Drug Administration, HFA-305
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 00N-1463; FDA Proposed Rule on Labeling Requirements for Systemic Antibacterial Drug Products Intended for Human Use (65 Federal Register 56511, September 19,2000)

Dear Sir/Madam:

Bristol-Myers Squibb is a diversified worldwide health and personal care company with principal businesses in pharmaceuticals, consumer medicines, beauty care, nutritionals and medical devices. We are a leading company in the development of innovative therapies for cardiovascular, metabolic, oncology, infectious diseases, and neurological disorders.

The Bristol-Myers Squibb Pharmaceutical Research Institute (PRI) is a global research and development organization that employs more than 4,300 scientists worldwide. PRI scientists are dedicated to discovering and developing best in class, innovative, therapeutic and preventive agents, with a focus on ten therapeutic areas of significant medical need. Currently, the PRI pipeline comprises more than 50 compounds under active development. In 1999, pharmaceutical research and development spending totaled $1.4 billion.

For these reasons, we are very interested in and well qualified to comment on the FDA proposal to issue a rule for Labeling Requirements for Systemic Antibacterial Drug Products Intended for Human Use.

00N-1463

C 6

BMS Comments on Proposal

Summary

We commend the U.S. FDA for their active interest in reducing antibiotic resistance. BMS welcomes collaboration with the FDA, PhRMA and other interested parties to address this important issue in an innovative approach that does not involve radical labeling changes. As currently written, proposed §201.24 threatens to decrease *all* use of antibiotics (not only inappropriate use) while failing to accurately identify appropriate use. Furthermore, inappropriateness of usage is not the only reason for the development of resistance, as the statements imply. Important considerations that reinforce the need for additional evaluation, clarification and revision are summarized below. These concerns are followed by recommendations that would not jeopardize patient compliance and safety. These options include increased education, an efficacy review of existing antimicrobial products and minor label changes to be implemented in a uniform and fair manner.

Introduction

Proposed rule §201.24 requires that various alerts regarding inappropriate use of antibiotics be placed throughout the label of antimicrobial products. The alerts state that prescribing of the drug product be guided by the identification of the causative microorganism and determination of its susceptibility profile. The intended goal of this regulation is to decrease the prevalence of drug resistance in microorganisms. This objective departs from the accepted concept that the purpose of the label is to educate the prescriber regarding safe and effective use of the specific product.

Specific Comments

Analysis of Proposed Label Changes

§201.24(a) places a warning against inappropriate use of antibiotics in the label location reserved for black-boxed Warnings that usually describes life-threatening adverse events.

- The placement of this message here dilutes the importance of this prominent location and may result in physicians paying less attention to black-boxed Warnings that deal with life-threatening issues. The content of this message is discussed further below under §201.24(d).

§201.24(b) promotes identification of the causative microorganism and determination of its susceptibility profile as required for appropriate use in the Clinical Pharmacology section.

- BMS believes that this labeling approach interferes with the practice of medicine since the choice of antibiotic treatment should be made by the physician after weighing the overall benefits and risks to the patient.

§201.24(c) repeats a similar message as §201.24(b) in the Indications and Usage section.

- This statement conflicts with the existing widely accepted practice guidelines that recommend empirical antibiotic treatment, particularly for outpatient infection. For example, the American Thoracic Society Guideline for Pneumonia specifically recommends empirical treatment of pneumonia and has concluded that Gram stains of sputum, cultures and susceptibility testing are not cost effective, particularly for outpatient infection.
- This guideline does not consider Outcome information analyzing the benefits of empiric antibacterial treatment in reducing morbidity and mortality.
- The wording fails to mention that antibiotic use for prophylaxis is within the standard of care and is found as an indication is several labels (i.e., mezlocillin, cefuroxime, metronidazole, etc.).

§201.24(d) repeats the same messages as §201.24(a) in the Precautions section and connects inappropriate use with decreased future effectiveness.

- This use of the verb "may" in this labeling proposal properly denotes the tenuous, circumstantial connection that supports the assumptions prevalent throughout this proposed rule and will be discussed further in the Scientific Issues section below. The radical nature of the label changes requires stronger evidence from the scientific community than currently exists.

§201.24(e) deals with Patient Information.

- The first statement recommends that patients be counseled to treat bacterial infections and not viral infections.
  - As written, this statement could suggest that patients are qualified and capable of diagnosing their own infections.
- The second recommendation urges the patient to follow their doctor's directions and is fully supported by BMS. Stating the rationale that refusal to do so may decrease the effectiveness is also a worthwhile statement.
- The last part of §201.24(e) warns that failure to follow directions will also give rise to untreatable bacteria.
  - As written, this statement can be misinterpreted and may inhibit patients from reporting serious adverse events to their doctor or even prevent them from starting therapy in the first place.

Scientific Issues

The rationale for the proposed FDA labeling changes has some sound scientific basis in terms of generalizations but the data may be taken out of context. For example, the statement that "...inappropriate use may increase the prevalence of the drug resistant organisms and decrease the effectiveness..." is accurate, but incomplete. Several factors are involved in the spread of drug resistance (i.e., improper hand washing, day care, veterinary use in livestock, etc.). The best practice of antibacterial agent prescribing and usage can still ultimately result in antimicrobial resistance because of the nature of selection stemming from normal physiological spontaneous mutation rates.

The estimation of risk for frequency of resistance emergence in the clinical setting is based on in vitro selection of resistant strains under laboratory conditions that may or may not mimic the situation in man. All antimicrobials have "built in obsolescence" and there will be natural progression for selection of resistance regardless of best practice usage. Consider an antibacterial agent with an intrinsic frequency of resistance emergence of 1×10^{-8} that is used to treat an infection with a population of pathogens in excess of 1×10^{-8}. The mathematical chance is that there will be a mutation selected that may lead to resistance emergence even in the presence of best practices for medicine. The significant differences in the in vitro frequency of resistance displayed by the various classes of antimicrobials suggest that this frequency can be further decreased with continued research.

One of the factors driving development of antimicrobials by the pharmaceutical business is the unmet medical need of antibiotic resistance. The development of resistance can be reduced by greater emphasis on pharmacodynamic factors, such as AUC/MIC and Cmax/MIC ratios. In addition, new generation antibiotics have been successfully designed, developed and promoted for the appropriate use of treating bacterial infections without generating resistance. For example, cefepime is less sensitive to beta-lactamases and has a high rate of porin penetration, thereby increasing susceptibility and decreasing resistance inducer capacity. Gatifloxacin has excellent PK and targets two bacterial proteins (DNA gyrase and Topoisomerase IV), thereby requiring multiple steps to acquire resistance. These attributes may provide 'resistance emergence suppression' to actually reduce the incidence of resistance emergence as compared to older agents. In addition to in vitro selection, the emergence of resistance is a result of complex factors relating to the intrinsic activity of the antimicrobial (i.e., permeability, efflux potential, pharmacokinetic and pharmacodynamic properties, static versus cidal mechanism, cellular target, etc.) and extrinsic considerations (i.e., target organism, health of the patient, type and site of infection, prior exposure to antibiotics, etc.). We need to constantly educate physicians to prescribe improved antibiotics that are tailored to the specific needs of the patient's over-all condition. The current proposal for restrictive labeling may hinder these efforts.

Quantifiable Benefits and Costs

The expense of the printing time and effort are underestimated from BMS's perspective because of the number of different presentations and the type of packaging for some of our antimicrobial products. The average cost of changing the label for BMS is $8.8K per product (as compared with the FDA's $2.2 K estimate). This estimate does not include the time spent by regulatory and quality control employees in review and approval of art work and production components. The total sum to implement §201.24 for 761 antimicrobial products would fall between FDA's conservative $2 million estimate and the $6.7 million as realistically calculated by BMS. This is a significant amount of money that could be used more creatively to address the issue in a constructive manner.

Recommendations:

BMS considers the proposed label changes unnecessary but recognizes the need to emphasize the threat of resistant microorganisms to the medical community. We recommend the following alternatives to address the problem:

- Invest the significant amount of money that would be required if §201.24 were to be implemented in an educational campaign sponsored by PhRMA to minimize irresponsible prescribing.
- Evaluate marketed antibiotics and retire older products with higher potential for inducing drug resistance (i.e., poor PK and/or potency, single step resistance development) in favor of newer antibiotics with optimized PK, potency and multiple step pathways required for resistance development.
- While we disagree with the need for any labeling revisions, if this rule is enacted, we advocate to limit the required labeling to the Precautions section and suggest the following wording:

General §201.24(d)

To help reduce the prevalence of drug-resistant microorganisms and maintain the effectiveness of XXXX and related antimicrobial agents, XXX should only be used to treat infections that are proven or strongly suspected to be caused by susceptible microorganisms.

Information for Patients §201.24(e)

Patients should be counseled about the differences between viral and bacterial infections. They should be informed that antimicrobial agents such as XXXX are ineffective against viral infections and that not following instructions for use of antimicrobial agents may decrease their effectiveness.

Patients should be told to take XXX exactly as directed. They should be instructed to not skip doses and to complete the full course of therapy, but to call their health care provider promptly if side effects occur.

- A final recommendation is that, regardless of the selected approach, the guidelines be uniformly enforced and embraced by the entire community, both medical and pharmaceutical, in a fair, simultaneous and seamless manner. This last requirement is critical for the success of this program since it will prevent confusion in the medical community.

BMS appreciates the opportunity to provide comment to the FDA and will also be respectfully requesting that FDA give consideration to our recommendations. We would be pleased to provide additional pertinent information as may be requested and to collaborate with you on this particular issue.

Sincerely,

Laurie Smaldone, M.D.
Senior Vice President
Regulatory Sciences & Outcomes Research

FOLD AND TEAR HERE

Thank you for using Return Receipt Service.

FROM:

SERV: CER

TRK#: P976263137

11/16/00
11:29

TO: HFA-511

2129

OF PCS: 1

7321024135986

RM: HFA-511

BMS-PG 1490-1

Bristol-Myers Squibb
Pharmaceutical Research Institute

P.O. Box 4000
Princeton NJ 08543-4000

Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane
HFA-305, Room 1061
Rockville, MD 20852

LINE 1

CERTIFIED

P 976 263 137